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Industrial Milestones in Organometallic Chemistry

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1.1 Definition of Organometallic and Metal–Organic Compounds

Organometallic compounds can be defined as compounds that contain at least one chemical bond between a carbon atom of an organic moiety and a metal. The metal can be alkaline, alkaline earth, transition metal, lanthanide, or a metalloid such as boron, silicon, and phosphorus. Therefore, metal–phosphine complexes are also often included in this category, although they do not contain a typical metal–carbon bond – they are more commonly referred to as “metal–organic compounds.” For the purposes of this book, applications of both organometallic and metal–organic compounds are discussed on the basis of “organometallic chemistry.”

1.1.1 Applications and Key Reactivity

The three major types of applications of organometallic compounds in industry are in the areas of electronics, polymers, and organic synthesis. In organic synthesis, the organometallic compounds are used as either catalysts or stoichiometric reagents.

1.1.1.1 Electronic Applications

For electronic applications typically, the organometallic complex is subjected to chemical vapor deposition (CVD) to form an appropriate thin layer or subjected to organometallic chemical vapor deposition (OMCVD) where the deposition ultimately occurs via a chemical reaction at the substrate surface to produce a high-quality material. The production of thin films of semiconductor materials is used, for example, for LED applications via metal–organic vapor-phase epitaxy (MOVPE) where volatile organometallic Me_3E ($\text{E} = \text{Ga, In, Al, and Sb}$) compounds are used as precursors. They react with ultrapure gaseous hydrides in a specialized reactor to form the semiconducting product as a crystalline wafer [1–23].

1.1.1.2 Polymers

Another major application for organometallic complexes is in the polymer industry. Three common types of polymers produced via catalysis are particularly noteworthy. Polysiloxanes, also known as silicone, are polymers made up of repeating units of siloxane [4]. They have widespread application in a large number of different fields ranging from cookware to construction materials (e.g. GE silicone), medicine, and toys. Pt-based catalysts are commonly applied in the silicone industry for the production of a variety of products [5]. A milestone in the history of organometallic chemistry in the industry was the discovery of the Ziegler–Natta catalyst and its application in polymerization reactions [6]. Ziegler and Natta were awarded the Nobel Prize for their work in this field in 1963 [7]. Another area that has been recognized for its importance is olefin metathesis for which a Nobel Prize has been awarded to Grubbs, Schrock, and Chauvin. This has been applied to synthesize polymers via ROMP (ring-opening metathesis polymerization) [8].

1.1.1.3 Organic Synthesis

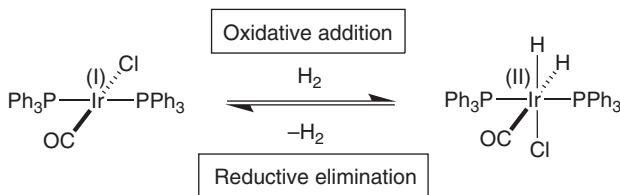
The focus of this book, however, is on the exploitation of organometallic compounds for organic synthesis, relevant to industry applications. One of the major applications in organic synthesis is catalysis.

In cases where the organometallic compound is used as a catalyst, for example in a process involving cross coupling, a precatalyst should be able to get activated to the active catalytic species to bind with the organic substrate(s), do the transformation, and release the product such that the active catalytic species returns to its original state in the catalytic cycle. During the organic transformation, the concentration of the catalyst can decrease with time because of poisoning. The efficacy and efficiency of the catalyst depend on how fast and how long it can retain its original activity. The turnover numbers (TONs) and turnover frequencies (TOF) are usually used to describe the activity of a catalyst. Organic chemists have started using organometallic compounds as catalysts to develop more efficient and practical processes [9–12].

The reactivity of organometallic complexes toward various reagents is the reason behind the widespread use of organometallic compounds as catalysts for a variety of organic transformations. The most important types of organometallic reactions are oxidative addition, reductive elimination, carbometalation, hydrometalation, β -hydride elimination, organometallic substitution reaction, carbon–hydrogen bond activation, cyclometalation, migratory insertion, nucleophilic abstraction, and electron transfer. In the following paragraphs, we will provide a brief overview of the basic theory with some selected applications.

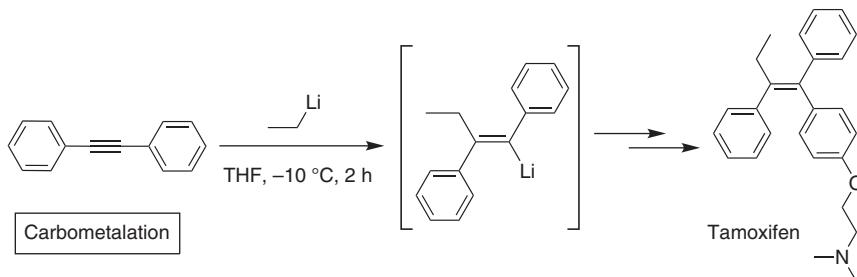
Oxidative addition involves the breakage of a bond between two atoms X–Y. Splitting of H_2 with the formation of two new metal–H bonds is an example of an oxidative addition process (Scheme 1.1). Reductive elimination is the reverse of this process. In an oxidative addition process, the oxidation state of the metal is increased by 2, whereas in reductive elimination, oxidation state of the metal is decreased by 2. Both steps are crucial for metal-catalyzed cross-coupling reactions, as the first and the last steps of the catalytic cycle. Several factors can affect these two steps. The structure of the ligand (phosphine or other molecules

coordinated with the metal), the coordination number of the metal in the complex, and the way in which the complex is activated to the catalytic species in the catalytic cycle, etc., can be modified and tailored to get the best outcome for a particular reaction [13]. The oxidative addition of H_2 onto Vaska's complex (Scheme 1.1) is a crucial step in metal-catalyzed hydrogenation reactions. The application of this methodology to industrially relevant molecules is further discussed in Section 1.3.3.



Scheme 1.1 Oxidative addition and reductive elimination.

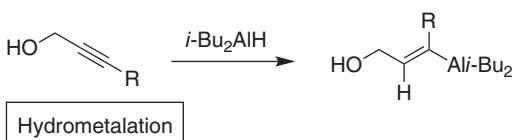
Carbometalation involves, as the name suggests, the simultaneous formation of a carbon–metal and a C–C bond. This is most commonly used to form a stoichiometric metal-containing reagent, such as the reaction between ethyllithium and bis-phenylacetylene in the synthesis of TamoxifenTM, a breast cancer drug (Scheme 1.2) [14].



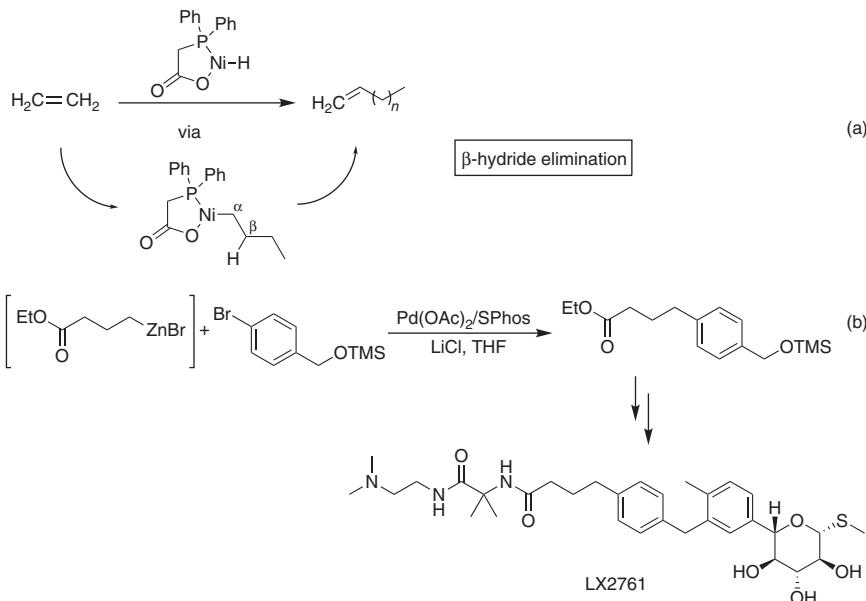
Scheme 1.2 Carbometalation as a key step toward the synthesis of TamoxifenTM.

Hydrometalation is similar to carbometalation, where, instead of a C–C bond, a C–H bond is formed alongside the carbon–metal bond. One such example is hydroalumination, where DIBAL ($i\text{-Bu}_2\text{AlH}$) is added across an alkyne (Scheme 1.3) [15]. This, similar to carbometalation, is most commonly a stoichiometric transformation with the aim of preparing an organometallic reagent that can be used as a reactant for subsequent desired transformations.

β -Hydrogen elimination, technically the reverse of hydrometalation, can in some cases result in the formation of undesired side products. In other cases, it is a “blessing” as the preferred reaction pathway. In Shell higher olefin process (SHOP), for the oligomerization to occur, a final β -hydrogen elimination reaction is performed to release the substrate from the catalyst (Scheme 1.4a) [16]. In the cross-coupling reaction between an aryl halide and an organometallic



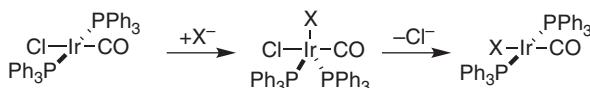
Scheme 1.3 Hydroalumination of alkynes.

Scheme 1.4 a) β -hydride elimination is exploited in the Shell higher olefin process (SHOP). b) sp^2-sp^3 cross-coupling in the synthesis of a diabetes drug.

reagent containing β -hydrogens, this reaction can form the undesired alkene side products, hence detrimental. This is the reason why sp^2-sp^3 coupling and sp^3-sp^3 coupling become very challenging even today. However, a few success stories of these types of cross-coupling reactions have been reported, such as sp^2-sp^3 Negishi reaction for the synthesis of LX2761, a diabetes drug by Lexicon Pharmaceuticals (Scheme 1.4b) [17].

Organometallic substitution reactions can occur either via an associative or a dissociative substitution mechanism. This can be compared to $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ substitution mechanisms in organic chemistry. The overall outcome in either case is an exchange of a ligand on the organometallic complex. Scheme 1.5 illustrates an associative substitution mechanism to exchange Cl for X on Vaska's complex. This complex does not have any significant references to being employed in industry as a catalyst, but studies of its reactivity has been vital in providing the conceptual framework for homogeneous catalysis [18].

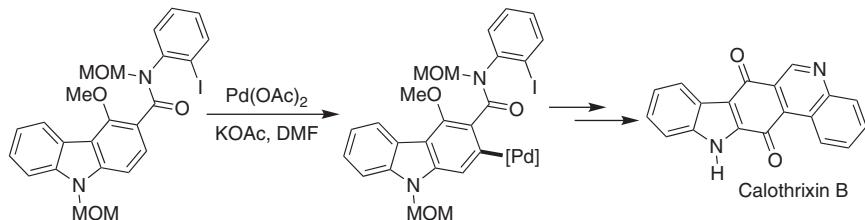
One of the reactions that has become increasingly exploited, particularly to complement the cross-coupling chemistry, is C–H activation. This is where the



Organometallic substitution reaction

Scheme 1.5 Organometallic substitution reaction exemplified by Vaska's complex. Source: Wilkins 1991 [24]. Reproduced with permission of John Wiley & Sons.

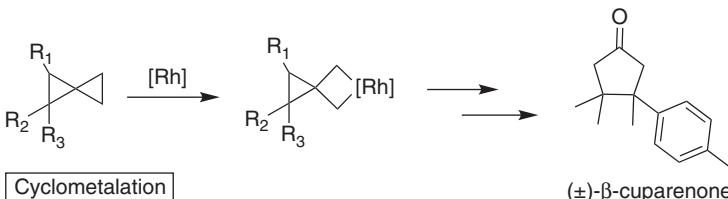
metal gets inserted into a C—H bond of the substrate. There are many different pathways for this to happen; it can be promoted and directed to the site of choice by using a directing group, such as the amide exemplified in Scheme 1.6. Iridium-catalyzed direct borylation reactions can also be considered as a type of C—H functionalization reaction. This type of reactions is further discussed in Section 1.3.2.1.



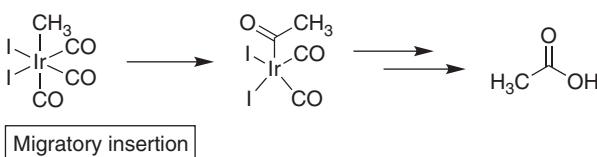
Carbon–hydrogen bond activation

Scheme 1.6 Carbon–hydrogen bond activation exemplified by the total synthesis of calothrixin B, which possesses various biological activities such as anti-malarial and anti-cancer. Source: Ramkumar and Nagarajan 2013 [25]. Reproduced with permission of American Chemical Society.

In cyclometalation reaction, the strain of certain motifs is often exploited to insert the metal into C—C bonds. One example is the Rh-catalyzed insertion into cyclopropanes to form metallacyclobutanes (Scheme 1.7). This has been applied in the total synthesis of (\pm) - β -cuparenone [19]. Metallacyclobutanes also form a very crucial part of the metathesis olefination mechanism, as deduced by Chauvin [20].



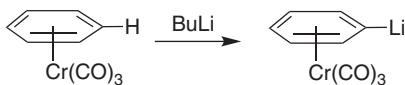
Scheme 1.7 Cyclometalation exemplified by the oxidative additions of Rh into a cyclopropane moiety.



Scheme 1.8 Migratory insertion exemplified by a step in the Cativa process.

Migratory insertion is crucial for any carbonylation reaction and is illustrated in Scheme 1.8 by a step in the iridium-catalyzed Cativa process, where methanol is converted into acetic acid [21]. The migration involves the insertion of one ligand (CO) into the metal–C bond (Ir–Me). The reverse reaction, decarbonylation of aldehydes to form an alkane with the release of CO, is also a reaction known to be catalyzed by Rh complexes [22], such as Wilkinson’s catalyst [23]. Migratory insertion is not restricted to CO alone but can also occur with SO₂, CO₂, and, most importantly, alkenes. The insertion of an alkene into an M–C bond is the key step in any oligo- or polymerization reaction, such as the Ziegler–Natta process [26].

Nucleophilic abstraction is a process when a ligand is fully or partly removed from the metal by the action of a nucleophile. In Scheme 1.9, the action of *n*-BuLi on a chromium-coordinated benzene ligand results in hydrogen abstraction [27]. Basically, the chemical reactivity of the ligand is altered when coordinated with a metal. This alters the reactivity of the ligated compound and may result in reactions that are not possible to carry out with the same non-ligated substrate.

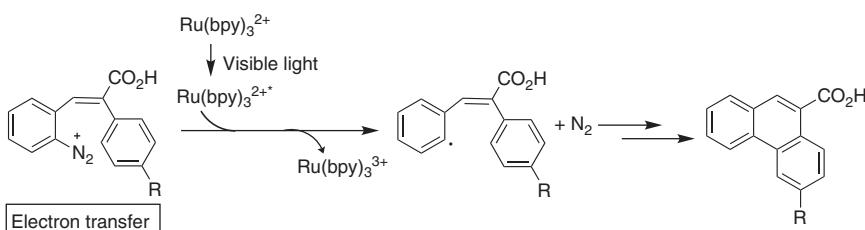


Nucleophilic abstraction

Scheme 1.9 Nucleophilic abstraction illustrated by hydrogen abstraction using *n*-BuLi.

Another important organometallic reaction to be discussed is electron transfer. The ability of certain organometallic complexes to initiate electron transfer reactions in combination with a visible light source has made some transformations possible that cannot be achieved using conventional chemistry. This is illustrated in Scheme 1.10 with one step in the photocatalytic Pschorr reaction using Ru(bpy)₃²⁺ as the photoredox catalyst [28, 29]. The phenanthrene formed can be further used for various purposes, such as in the manufacture of dyes, pharmaceuticals, etc. [30]. The potential of metal-catalyzed electron transfer reactions forms the basis for a new area in organic synthesis with lot of potentials [31].

Exploitation of the wide variety of “organometallic reactivity” has made the field of organometallics one of the most applied areas in process chemistry with particular importance to the pharmaceutical, agrochemical, polymer, and fine chemical industries.



Scheme 1.10 Electron transfer illustrated by one step in the photocatalytic Pschorr reaction to form phenanthrene.

1.2 Industrial Process Considerations

Organometallic compounds are routinely prepared and used as stoichiometric reagents or catalysts for a range of synthetic processes on a multikilogram scale or even a ton scale.

In order to operate a commercially viable industrial chemical process, a reliable chemical synthesis route is needed as well as an understanding of how a process will behave during the scale up by taking into consideration factors such as heat and mass transfer, mixing, particle size, and filterability, etc. Air, moisture, and thermal sensitivity of some of the organometallic complexes or their intermediates needs to be addressed with proper handling techniques including inert conditions to achieve the maximum process efficiency and process safety. In addition, incorporation of environmental impact of the process is also very important, where exposure of chemicals and solvents and waste generation need to be minimized.

It is important to have a scalable chemical process, usually optimized on a bench scale to produce milligram to gram and then transferred to the pilot plant, typically to a kilogram scale. During this transfer, typically, one needs to readjust the rate of reagent addition to manage the exotherm, rate of agitation, rate of heating, degassing cycles, reaction time, etc. Identifying the optimal catalyst with the minimal loading especially when one uses *platinum group metals* (PGMs) in conjunction with expensive ligands is also important. Even for a well-known organic transformation such as a Pd-catalyzed cross-coupling, the process will not be economical if the reaction is poorly optimized, considering metal loss, purification of the products, and waste disposal. A proper understanding of the thermodynamics and kinetics is also important.

Experience in using DOE coupled with a “knowledge-based” process approach can accelerate the process development. It is important to involve both chemists and chemical engineers during the scale-up and process optimization, considering the equipment design, safety, raw material selection, etc. Even if the precatalyst is not sensitive to air, one has to conduct the reactions under inert conditions as the “active catalytic species” in the cycle might be sensitive to air. This can not only minimize the by-product formation but also increase the life cycle of the catalyst and hence the TONs and TOFs.

The kinetic control of an organometallic process can be another important factor. One example is low-temperature reactions involving organolithium reagents, where it is essential to avoid significant decomposition of thermally sensitive species, thermal promotion of undesired side reactions, and control the reactivity of exothermic processes.

Treatment of waste streams from organometallic processes must be considered carefully as they may contain precious metal or even other transition metal residues originating from the decomposition of the organometallic compounds. Apart from the well-documented environmental impact of PGM compounds, finely divided PGM particles, if allowed to dry out, pose a significant fire hazard. Because of the significant environmental hazards associated with heavy metal residues, predominantly arising from their persistence in the biosphere via bioaccumulation, generation of this type of waste stream on production scale should be avoided wherever possible, with environmental regulations strictly controlling the level of any emissions. Some common catalyst precursor complexes release harmful side products when activated or substituted. For instance, $[\text{Pd}(\text{COD})(\text{Cl})_2]$ releases 1,5-cyclooctadiene (COD) in the presence of phosphines, which, among its other chemical hazards, has a pungent odor even in low concentrations. Therefore, extreme care must be taken when dealing with process waste that contains it. Similarly, many of the metal carbonyl compounds can generate CO gas, which needs to be properly vented. Some of these carbonyl-based compounds undergo sublimation as well.

1.3 Brief Notes on the Historical Development of Organometallic Chemistry for Organic Synthesis Applications Pertaining to the Contents of this Book

Most organometallic processes have evolved and developed from seminal discoveries in the late 1800s or early 1900s. In some cases, it is easier to pinpoint the exact seminal reports, whereas in other cases, this task is not so easy. Sabatier's report of nickel-catalyzed hydrogenation can easily be identified as the discovery of metal-catalyzed hydrogenation reactions [32], for which he got the Nobel Prize in Chemistry in 1912. For the cross-coupling area, its origin is slightly more difficult to deduce precisely although our 2012 review articles and book provide a much better understanding of the area [9, 10, 13, 33, 34]. One could argue that it dates back to 1912 Nobel laureate Victor Grignard's discovery of RMgX reagents, where Grignard shared the Nobel Prize with Sabatier. Although both technologies (Grignard in 1912 and cross-coupling in 2010) got Nobel Prizes, the former is considered to be a "breakthrough innovation," whereas the latter is called "incremental innovation." The impact of cross-coupling in chemical processes shows its significance by being awarded the Nobel Prize, in comparison to many competing technologies.

In this section, we will briefly go through the origins of a few prominent areas within organometallic chemistry and how they relate to the current industrial applications with respect to the topics covered by the chapters in this book.

1.3.1 Synthesis of Stoichiometric Organometallic Reagents

1.3.1.1 Conventional Batch Synthesis

Arguably, the most important stoichiometric organometallic reagents are organolithium compounds, RLi . The studies of these reagents were pioneered by Karl Ziegler, Georg Wittig, and Henry Gilman [35]. Their relatively straightforward preparation, high basicity, and wide array of functionality provide convenient access to useful synthetic routes such as metalation, deprotonation, carbolithiation, and transfer or exchange of the nucleophilic organic fragment R^- .

In 1899, by substituting Mg for Zn in alkylation reactions, Philippe Barbier's student Victor Grignard (Figure 1.1) developed the $RMgX$ alkylating agents that bear his name to this day. Being a less sensitive but more potent source of alkyl anions than their Zn-based counterparts, Grignard showed how they can efficiently alkylate carbonyl compounds, a discovery that proved to have huge impact in synthetic chemistry and earned him a Nobel Prize in 1912 [36].

Today, Victor Grignard is remembered as the father of organometallic chemistry. Organomagnesium compounds represent very useful alternatives to their lithium counterparts, exemplified by the widespread use of Grignard reagents, $RMgX$, for efficient alkylations and arylations. These reagents are now produced in multiton quantities. Organocalcium compounds are more reactive alkyl sources than Grignard reagents, but their applications are limited because of the increased difficulty of their preparation and the thermal instability they exhibit. Organocalcium compounds have also shown promise as hydroamination catalysts. In comparison to organolithium and organomagnesium, organoaluminum compounds, R_3Al reagents, are generally far less effective stoichiometric reagents but do add to alkenes and alkynes with high regio- and stereoselectivity via carboalumination. Importantly, however, they have found particular use as a vital component of the heterogeneous Ziegler–Natta polymerization process for the industrial-scale production of polyethylene and polypropylene. Aluminum

Figure 1.1 Victor Grignard. Source: <https://commons.wikimedia.org/w/index.php?curid=545837>. Licensed under CC BY 3.0.



alkyls are also widely utilized for group III–V chemistry for the production of electronic materials via CVD.

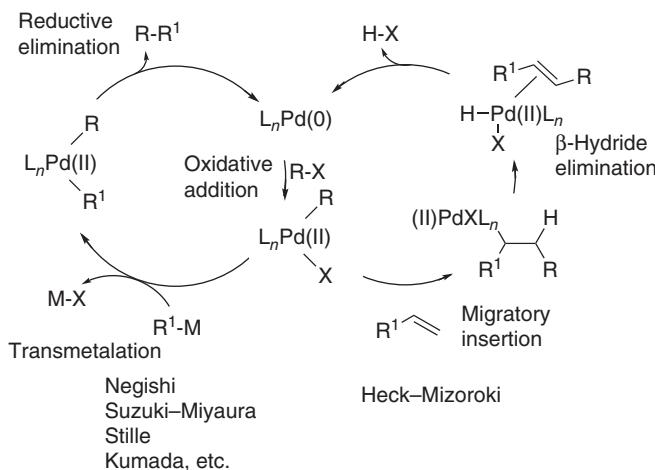
1.3.1.2 Organometallics in Flow

Industrial-scale organic synthesis for fine chemical applications, such as natural products or active pharmaceutical ingredients (APIs), and organometallic syntheses have traditionally been conducted in batch using large-volume ($>100\text{ l}$) reactors. In continuous flow processes, small amounts of reagent solutions are continuously pumped along a flowing stream to mix at a specific junction with resonance time to react them together to yield the product, which is being purified under the flow conditions and collected. In some cases, a cascade approach has been considered where multiple reagents have been mixed sequentially rather than performing reactions in different batch reactors. Industries have been using this technique for the manufacture of petrochemicals and bulk chemicals as this approach has proven to be not only most economical but also produce good-quality products consistently. The recent interest in flow chemistry in academia for the synthesis of more complex organic compounds has increased efforts to apply this rapidly burgeoning technology both in fine chemical and pharmaceutical industries. The advantages that flow processes can bring in a commercial context relative to batch production are shorter reaction times, greater temperature control, rapid optimization, shorter path length for photochemical reactions, and improved process safety. Chapter 2, authored by Joseph Martinelli of Eli Lilly, presents the design, development, and implementation of an API manufacturing route under continuous flow conditions to showcase the application of this technology in organic synthesis. Chapter 3 details the lithiation and borylation chemistry under flow, as developed by Joerg Sedelmeier and Andreas Hafner at Novartis. This chapter provides a snapshot of how this technology can also be applied for the synthesis of organometallic reagents.

1.3.2 Cross-coupling Reactions

Several years after Grignard's discovery of RMgX reagents, in 1941, Kharasch undertook the first systematic investigation of transition-metal-catalyzed sp^2 – sp^2 carbon coupling, detailing the observation of homocoupling of Grignard reagents [37, 38]. Subsequent research from his group led to the earliest report of a cross-coupling reaction, where a cobalt-based catalyst was used to couple vinyl bromide with an aryl Grignard reagent [39]. This made him to be the father of cross-coupling reactions.

The metal catalysts in question are also organometallic complexes that mediate the coupling of two different hydrocarbon fragments for organic synthesis purposes in the fine chemical, agrochemical, and pharmaceutical industries. A simplified catalytic cycle is shown in Scheme 1.11. Many of the key reactivity steps that are characteristic for organometallic complexes are a prerequisite for these reactions to take place. Initial oxidative addition is followed by transmetalation (organometallic substitution) and finally reductive elimination to form the



Scheme 1.11 Simplified catalytic cycles for cross-coupling reactions.

desired product and regenerate the catalyst. Each of these steps has been the subject of a number of studies to try and understand the exact nature of their mechanism. For Suzuki–Miyaura reactions, the transmetalation step has been the focus of attention of several research groups. The Denmark, Lloyd-Jones, and Hartwig groups have independently studied this step of the catalytic cycle for these types of cross-coupling reactions [40–42]. In Sonogashira reactions ($sp-sp^2$ bond formation), a Cu cocatalyst is commonly employed [43]. In many recent refinements of this reaction, however, the need for a cocatalyst has been circumvented by, for example, a careful choice of Pd catalyst and reaction conditions [44–46]. The mechanism of the Heck reaction differs from the other named cross-coupling reactions in that a β -hydrogen elimination is crucial for the formation of the final product.

Many pioneers have played a role in the development of this area and lent their names to the reactions they have discovered. The importance of cross-coupling to the field of chemistry was ultimately recognized in 2010 by awarding the Nobel Prize to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for their research efforts in palladium-catalyzed cross-couplings in organic synthesis [9, 10, 13, 35, 36]. Cross-coupling is an example where incremental innovation is of equal importance to the breakthrough discovery, significant enough even for the award of the Nobel Prize.

Following from an earlier work by Fujiwara, in 1969, Richard Heck published the first examples of cross-coupling using stoichiometric palladium(II). Building on a separate work by Mizoroki, he proposed the first Pd(0)-mediated catalytic cycle for the cross-coupling of iodobenzene and styrene, opening the door for an explosion of discoveries in Pd-catalyzed cross-coupling chemistry. The traditional Mizoroki–Heck reaction forms a substituted alkene via cross-coupling of an unsaturated halide or pseudo-halide with an alkene under Pd catalysis and is frequently employed for C–C coupling in industrial settings. The Heck mechanism can also be accessed using nickel to mediate the catalysis. Under

certain conditions, this brings advantages relative to the palladium version, such as higher activity. This is thought to be because of lower energy barriers to crucial steps in the catalytic cycle and greater selectivity to the desired product because of the greater efficiency of undesirable β -hydride elimination for Pd vs Ni. One example of successful implementation and scale-up of a nickel-catalyzed Mizoroki–Heck reaction at BI is discussed in detail in Chapter 4 by Jean-Nicolas Desrosiers and Chris H. Senanayake. This chapter is also relevant in terms of the emerging area of the use of base metal instead of precious metal catalysis.

The Suzuki–Miyaura reaction, where a boronic acid/ester is coupled to a halide or pseudo-halide precursor under palladium-mediated catalysis, is the most common C–C coupling reaction in industry. Suzuki couplings are advantageous at a large scale because of the mild reaction conditions, the commercially available and relative environmentally benign boronic acid/ester starting materials, and the comparative ease of disposal of boron-containing by-products compared to processes using other organometallic reagents.

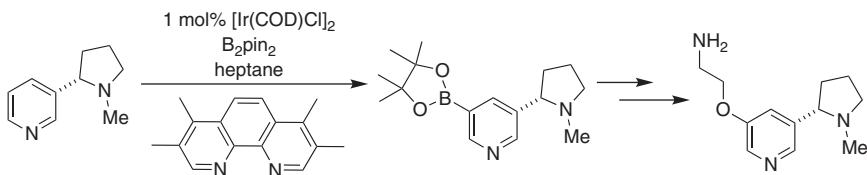
The Kumada cross-coupling reaction utilizes a Grignard reagent and an organic halide as precursors and classically operates under palladium or nickel catalysis. Although demonstrated to be a largely efficient C–C bond formation strategy, Kumada couplings can be problematic in large-scale synthesis because of the high reactivity of Grignard reagents, which exhibit limited functional group tolerance. However, there is a new trend where palladium catalysts are substituted for those containing iron, advantages of which include lower cost of the metal because of higher earth abundance and lower toxicity. Although still relatively new, the iron-catalyzed Kumada coupling represents a rapidly growing area of organometallic synthesis with great industrial potential, which is discussed in Chapter 5, authored by Rakeshwar Bandichhor of Dr Reddy's Laboratories. Similar to the nickel-catalyzed Mizoroki–Heck reaction detailed in Chapter 4, Chapter 5 provides another example of the industrial trend in switching from precious metal to earth-abundant metal catalysis.

Overall, the breadth of catalytic cross-coupling reactions has found significant application in the field of organic synthesis for the production of pharmaceutically and agriculturally relevant molecules, often employed in several steps as part of a multistep synthesis. Under carefully optimized conditions, these catalysts typically offer advantages over stoichiometric alternatives such as high selectivity, mild reaction conditions, functional group tolerance, low loadings, and avoidance of protecting groups. In cases where the metal-catalyzed cross-coupling reaction takes place in the end game of a total synthesis, it is important to determine the levels of residual metal in the final API. There are well-defined limits for each metal and how much a drug can legally contain [47]. In general, homogeneous cross-coupling catalysts cannot be recycled, although the metal itself can be recovered from the waste stream.

1.3.2.1 C–H Bond Activation

In 1983, Robert Bergman and William Graham independently detail the first transition-metal-mediated intermolecular C–H activation of alkanes by oxidative addition by pentamethylcyclopentadienyl–iridium(I) complexes [48, 49]. This opened up the possibility of carrying out cross-coupling reactions

where only one cross-coupling partner, or in rarer cases, neither of the two cross-coupling partners, is pre-functionalized as an aryl (pseudo)halide or an organometallic reagent. Noteworthy efforts within this field have been reported by the research groups of Keith Fagnou and coworkers [50], Melanie Sanford and coworkers [51], Christina White and coworkers [52], and Jin-Quan Yu and coworkers [53]. One class of reaction that falls under the C–H activation category is direct arylation of aromatics or heterocycles. In this type of chemistry, the heterocycle is nonfunctionalized and the successful reaction relies on the inherent nucleophilicity of the substrate or inherent acidity of certain C–H bonds in the molecule in order to achieve regioselectivity. Another breakthrough discovery in this area is the iridium/bipyridine-catalyzed direct borylation, first reported by Hartwig and coworkers [54]. This methodology was recently employed by Pfizer to form a nicotine analog (Scheme 1.12) [55].



Scheme 1.12 Iridium-catalysed direct borylation in Pfizer's synthesis of a nicotine analog.

Several other metal complexes based on, e.g. Pd or Ru have been successfully employed in C–H activation or direct arylation reactions. Chapter 6, authored by Collin Chan, Albert J. DelMonte, Chao Hang, Yi Hsiao, and Eric M. Simmons from BMS describes an intramolecular Pd-catalyzed direct arylation reaction that was used in the manufacturing route of Beclabuvir. Ru complexes are also emerging as alternative, or complementary, catalysts to the Pd ones for the purpose of CH activation chemistry. Anita Mehta of Chicago Discovery Solutions describes her experience of Ru-catalyzed direct arylation reactions in water in Chapter 7.

1.3.2.2 Carbonylation

Transition-metal-catalyzed carbonylation (introduction of CO) of methanol has been employed very successfully in the large-scale manufacture of acetic acid in the Monsanto process, which uses an anionic Rh carbonyl catalyst [56]. This process has since been superseded by the more economical and environmentally friendly Cativa process, which relies on an analogous iridium-based catalyst system [21, 57]. Pd catalysts have also been employed in carbonylation chemistry, which is now a widely applied methodology in the pharmaceutical industry [58].

1.3.2.3 Catalysis in Water – Micellar Catalysis

Despite the widespread use of palladium-catalyzed cross-coupling both in research and in production, for some of the more problematic transformations such as the arylation of nitroalkanes, most or all of the process conditions can require organic solvents, a dry/inert atmosphere, elevated temperatures, and

high catalyst loadings. A promising alternative to conventional cross-coupling conditions for which the former factors are requisite is micellar catalysis, whereby a surfactant is dispersed in aqueous media and the internal conditions of the micelles formed mimic organic solvents in which the substrates and the catalyst are compatible and the catalysis takes place. Care must be taken to select a surfactant that is environmentally benign and can interact with hydrophilic and hydrophobic functionalities (amphiphilic), whose polarity can accommodate the reagents to maximize the catalytic activity. The choice of catalyst itself is also important, as greater lipophilicity permits a lower catalyst loading. For organic synthesis on an industrial scale, micellar catalysis could confer major advantages in process safety, cost, and waste remediation, which is examined in Chapter 8 by Sachin Handa.

1.3.3 Hydrogenation Reactions

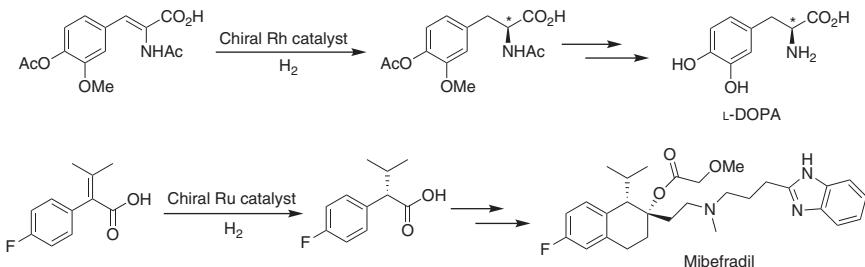
In 1900, French chemist Paul Sabatier first defined homogeneous and heterogeneous catalysis [59]. Together with Senderens, he discovered that the use of a trace amount of nickel as a catalyst promotes the hydrogenation of carbon compounds, and his work inspired others to develop the hydrogenation of fats, central to advances in the food industry [60]. He later shared a Nobel Prize with Grignard in 1912 for his work.

In 1922, Franz Fischer and Hans Tropsch reported the heterogeneously catalyzed production of linear alkanes and olefins from a mixture of CO and hydrogen (syngas) largely without oxygenated by-products. The process was so successful that it was later industrialized in 1925. In 1938, the German chemist Otto Roelen, during his investigation into the Fischer–Tropsch process, discovered that olefins can be catalytically converted to aldehydes in a process known as hydroformylation or the oxo process [61]. A $\text{Co}_2(\text{CO})_8$ catalyst was used to affect the conversion with the H_2/CO syngas feedstock. Now, the industrial-scale production of most useful synthetic aldehydes from alkenes is achieved via this process, traditionally under Rh- or Co-catalyzed conditions. The products can be hydrogenated to produce alcohols or used directly as starting materials in the organic synthesis of complex pharmaceutical agents [62]. Another process employing olefin as a raw material is the Wacker process. This involves the catalytic oxidation of ethylene to acetaldehyde and is one of the first Pd-catalyzed homogeneous processes on an industrial scale [63, 64].

Continuing the hydrogenation thread, in 1965, Wilkinson and Coffey reported the catalytic activity of $[\text{RhCl}(\text{PPh}_3)_3]$ for the homogeneous hydrogenation of alkenes [65, 66]. This discovery formed the basis for the development of asymmetric homogeneous hydrogenation as exemplified by the chiral Noyori-type ruthenium catalysts [67]. In 2001, William Knowles, Ryoji Noyori, and Karl Barry Sharpless were awarded the Nobel Prize in Chemistry for their work on enantioselective metal-catalyzed hydrogenation and oxidation reactions [68].

Asymmetric hydrogenation – the addition of two H atoms preferentially to one of the two faces of a prochiral unsaturated molecule – is a very important tool in the manufacture of bioactive pharmaceuticals and agrochemicals. The enantioselectivity derives from the chirality of the ligand bound to the metal

(commonly ruthenium or iridium) center in the active catalyst. The substrate is oriented relative to the chiral ligand in the catalyst–substrate complex to minimize steric interactions, and hydrogen is delivered to the sterically least hindered face. Asymmetric hydrogenation was first successfully applied to the industrial-scale manufacture of L-Dopa (Scheme 1.13) [69], and a treatment for Parkinson's disease aided by the explosion in the availability of chiral catalysts in the 1990s has since been used in the production of a range of pharmaceuticals, such as the calcium channel blocker *mibepradil* (Scheme 1.13) [70]. In Chapter 9, authored by Stephen Roseblade of Johnson Matthey, the aspects of asymmetric homogeneous hydrogenation and details of its application in several industrial cases are discussed.



Scheme 1.13 The application of asymmetric hydrogenation in the syntheses of L-DOPA and mibepradil.

1.3.4 Olefin Formation Reactions

1.3.4.1 Wittig Reaction

In 1954, Georg Wittig discovered the olefination reaction that bears his name [71]. The transformation used a new nucleophilic carbon source, a dipolar phosphonium ylide, to convert carbonyl compounds into alkenes (Scheme 1.14).



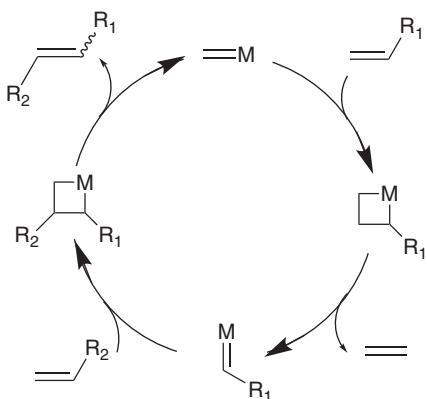
Scheme 1.14 Wittig olefination.

Wittig's work later earned him the Nobel Prize in Chemistry in 1979. To this date, no real viable solution has been presented to turn this into a catalytic version that could eliminate the problem of the large amount of phosphine oxide side product that is generated.

1.3.4.2 Metathesis Reactions

In 2005, Yves Chauvin, Robert Grubbs, and Richard Schrock won the Nobel Prize in Chemistry for the development of the metathesis method in organic synthesis. Most commonly, the catalysts used for metathesis reactions are based on ruthenium or molybdenum. The key intermediates in the catalytic cycle are a series of

metallacyclobutanes initiated from the reaction between the carbene-containing catalyst and one of the starting olefins (Scheme 1.15).



Scheme 1.15 General catalytic cycle for Metathesis reactions.

Olefin metathesis is finding increasing use in drug discovery and process chemistry on a commercial manufacturing scale, and with developments in catalyst systems, highly functionalized substrates can now be targeted. Exemplified by the first (publicly disclosed) case in the pharmaceutical industry to apply metathesis at scale, namely the hepatitis C drug candidate *ciluprevir* [72], chemists are able to access increasingly diverse chemistry on scale. Industrially relevant metathesis chemistry is discussed by John Phillips of Materia in Chapter 10.

1.3.4.3 Dehydrative Decarbonylation

Because of the ubiquity of carboxylic acids in industrial feedstocks obtained from biomass processing, such as the fatty acids, citric acid, and itaconic acid, an efficient method of transforming these groups into useful alkene functionalities, particularly linear olefins for the production of important polymers, is an attractive synthetic objective. Such a process – dehydrative decarbonylation – is traditionally achieved with palladium, rhodium, iridium, or nickel catalysts and can provide value-added odd-numbered alpha olefins desirable in the large-scale production of polymers, lubricants, and surfactants, from renewable even-numbered natural fatty acids. Dehydrative decarbonylation is discussed in by Alex John at California State Polytechnic University in Chapter 11.

1.3.4.4 Olefins as Starting Materials

Nucleophilic addition chemistry to an alkene is regarded as a fundamental methodology for organic synthesis; however, unactivated alkenes do not demonstrate this chemistry because of their lack of polarity. Substitution of the alkene with a carbonyl functionality such as in α,β -unsaturated carbonyl compounds renders the β position electrophilic by resonance and amenable to reaction with nucleophiles. With an appropriately selected nucleophile, conjugate addition results in C–C bond formation, saturation of the former olefin, and retention of the carbonyl group for further reactivity, thus is a very useful transformation in the synthesis of complex organic molecules relevant to the fine chemical and

pharmaceutical industries. As stereocontrol is so important, practical catalytic methods that confer this are highly desirable for large-scale processes, and rhodium systems incorporating chiral ligands have shown particular utility in affecting enantioselective conjugate additions [73].

1.3.5 Poly- or Oligomerization Processes

In 1955, German Karl Ziegler and Italian Giulio Natta developed a process to produce stereoregular polymers from 1-alkenes on a commercial scale [74]. The catalyst class that bears their name generally comprises silica-supported titanium halides and alkyl aluminum activators, capable of polymerizing propylene and other 1-alkenes to highly crystalline isotactic polymers.

The Ziegler–Natta (ZN) polymerization process has been widely industrialized to provide almost the entire global supply of polyethylene and polypropylene. By contrast to the more dominant heterogeneous ZN system, which employs silica-supported titanium tri- or tetrachloride with added organoaluminum activators, homogeneous ZN catalysis generally employs a metallocene catalyst of the type $[\text{Cp}^R_2\text{MCl}_2]$ (Cp^R = cyclopentadienide derivative, M = Ti, Zr, and Hf) alongside a methylaluminoxane (MAO) activator. The homogeneous ZN system enables a structural control at the molecular level that is not available to heterogeneous ZN catalysts via the constrained geometry of the organometallic complex. Non-metallocene-based ZN catalysts incorporate a wide range of alternative ligand types bearing heteroatoms that impart different steric constraints at the metal center, leading to divergent polymerization regimes.

1.3.6 Photoredox Catalysis for Organic Synthesis

In recent years, there has been an increasing interest in the development of synthetic applications of photoinduced electron transfer chemistry [75, 76]. This technology has also been adopted by industrial teams and demonstrated in a number of research publications [77, 78]. The catalysts of choice for this type of reactions are in general Ru- or Ir-based organometallic complexes with bipyridine- or phenylpyridine-based ligands.

1.4 Conclusion and Outlook

The use of organometallic complexes as catalysts or stoichiometric reagents has revolutionized the way organic molecules are being synthesized in the pharmaceutical, agrochemical, and fine chemical industries. This has not been an overnight change but a very gradual development starting from an initial discovery followed by incremental improvements and modifications. Cross-coupling reactions such as Suzuki–Miyaura are good examples of this.

Without any doubt, the growing requirements for greener, more efficient, and streamlined processes in industry will lead to further development and refining of current technologies. In some cases, well-established organometallic reactivity can be exploited for the purpose of carrying out organic transformations in a new manner. The emerging area of photoredox catalysis in cross-coupling reactions is a good example. Another area, where similar developments are ongoing,

is that of electrochemistry in organic synthesis. In other cases, it may be chemical engineering breakthroughs that make a major contribution to more efficient processes. Continuous processes carried out in flow reactors showcase examples of this emerging technology.

There is also a growing trend of working toward displacing precious metals by earth-abundant, metal-based catalysts. Although this is an achievable target for certain transformations, this is still to be established as a general viable alternative. One thing is certain; organometallic chemistry in the industry, whether as catalysts or stoichiometric reagents or whether transition metals or base metals, will remain the strongest pillar in organic synthesis especially from the perspective of process chemistry.

Biography



Carin C.C. Johansson Seechurn carried out her undergraduate studies at U.M.I.S.T. (University of Manchester Institute of Science and Technology), including a year abroad at CPE (l'Ecole Supérieure Chimie, Physique, Electronique de Lyon) in France to receive her MChem with French in 2003. She then joined the University of Cambridge, UK, where she received her PhD. degree in the area of organocatalysis working under Dr Matthew Gaunt.

After the completion of the Ph. D studies in 2006, she continued research with Dr. Gaunt, now in the area of palladium catalysis. In 2008, she joined the Catalysis and Chiral Technologies division of Johnson Matthey in the United Kingdom, based at Royston. In 2019, she moved to Cambridge. Carin is involved in the development, scale-up, and commercialization of new homogeneous metal catalysts. She is a coauthor of a number of publications, book chapters, and patents on the topic of homogeneous catalysis.



Ben M. Gardner, having obtained a first-class undergraduate masters' degree in Chemistry in 2008, Ben was awarded his PhD degree from the University of Nottingham in 2012 under the supervision of Stephen T. Liddle, his thesis entitled "The Chemistry of Uranium Triamidoamine Complexes." He continued to work in the Liddle group as a post-doctoral researcher investigating various aspects of non-aqueous synthetic actinide chemistry until 2016 when he took up the position of research chemist in the Homogeneous Catalysts division of Johnson Matthey plc. based in

Royston, UK, where he worked in the development and scale-up of precious metal catalysts. In 2018, Ben took up his current position of scientist at Cambridge Display Technology Ltd., where he is developing new conductive materials for organic electronics applications.



Thomas J. Colacot is working at Millipore Sigma (a business of Merck KGaA, Darmstadt, Germany) since May 2018 in the United States as an R&D Fellow, Director – Global Technology Innovation (Lab and Specialty Chemicals). His expertise is in the areas of new product and technology development; process R&D; scale-up; and tech transfers of organic, organometallic, and fine chemicals relevant for pharmaceutical, electronic, and biological applications with very strong interactions/partnership with customers. Before this, he worked as a global R&D manager/technical fellow in Homogeneous Catalysis of Johnson Matthey. He is considered to be one of the leading industrial experts in cross-coupling. He is a coauthor of about 100 articles, which include reviews, peer-reviewed publications, and books such as “New Trends in Cross-Coupling: Theory and Applications” (RSC) and “Organometallics in Process Chemistry – Topics in Organometallic Chemistry” (Springer, in process). He has also given over 400 presentations in national and international conferences, universities, and chemical and pharmaceutical companies. He is a member of many national committees and a visiting professor at IIT Bombay, Mumbai. His contributions to the field have resulted in many awards and accolades, some of which are the 2017 Catalysis Club of Philadelphia award for the outstanding contributions in catalysis, 2015 American Chemical Society National Award in Industrial Chemistry, 2015 IPMI Henry Alfred Medal, 2016 Chemical Research Society of India CRSI medal, 2016 IIT Madras Distinguished Alumnus Award, and Royal Society of Chemistry 2012 Applied Catalysis Award and Medal. In 2018, Merck KGaA recognized him as globally one of the most outstanding researchers. Thomas holds a PhD degree in Chemistry with an MBA degree and is a fellow of the Royal Society of Chemistry.

References

- 1 Ostroverkhova, O. (2016). *Chem. Rev.* 116: 13279–13412.
- 2 For seminal publication, see: Tang, C.W. and Vanslyke, S.A. (1987). *Appl. Phys. Lett.* 51: 913–915.
- 3 Singh, D., Nishal, V., Baghwan, S. et al. (2018). *Mater. Des.* 156: 215–228.
- 4 Mark, J.E., Schaefer, D.W., and Lin, G. (2015). Types of polysiloxanes. In: *The Polysiloxanes*, 32–67. New York: Oxford University Press.
- 5 Lewis, L.N., Stein, J., Gao, Y. et al. (1997). *Platinum Met. Rev.* 41: 66.
- 6 Hoff, R. and Mathers, R.T. (eds.) (2010). *Handbook of Transition Metal Polymerization Catalysts*, Onlinee. Wiley.
- 7 Claverie, J.P. and Schaper, F. (2013). *MRS Bull.* 38: 213–218.
- 8 Choinopoulos, I. (2019). *Polymers* 11: 298–329.
- 9 Johansson Seechurn, C.C.C., DeAngelis, A., and Colacot, T.J. (2015). Introduction to new trends in cross-coupling. In: *New Trends in Cross-Coupling – Theory and Applications* (ed. T.J. Colacot), 1–19. Cambridge: RSC.

- 10 Gildner, P.G. and Colacot, T.J. (2015). *Organometallics* 34: 5497–5508.
- 11 Hagen, J. (2015). Homogeneous catalysis with transition metal catalysts. In: *Industrial Catalysis: A Practical Approach*, 17–46. Weinheim: Wiley-VCH.
- 12 Klein, A., Goldfuss, B., and van der Vlugt, J.-I. (2018). *Inorganics* 6: 19–22.
- 13 DeAngelis, A. and Colacot, T.J. (2015). *New Trends in Cross-Coupling – Theory and Applications*, 20–90. Cambridge: RSC.
- 14 McKinley, N.F. and O'Shea, D.F. (2006). *J. Org. Chem.* 71: 9552–9555.
- 15 Wilke, G. and Müller, H. (1956). *Chem. Ber.* 89: 444.
- 16 Keim, W. (2013). *Angew. Chem. Int. Ed.* 52: 12492–12496.
- 17 Sirois, L.E., Zhao, M.M., Lim, N.-K. et al. (2019). *Org. Process. Res. Dev.* 23: 45–61.
- 18 Vaska, L. and DiLuzio, J.W. (1962). *J. Am. Chem. Soc.* 84: 679–680.
- 19 Matsuda, T., Tsuboi, T., and Murakami, M. (2007). *J. Am. Chem. Soc.* 129: 12596–12597.
- 20 Chauvin, Y. (2006). *Angew. Chem. Int. Ed.* 45: 3740–3747.
- 21 Sunley, G.J. and Watson, D.J. (2000). *Catal. Today*. 58: 293–307.
- 22 Kreis, M., Palmelund, A., Bunch, L., and Madsen, R. (2006). *Adv. Synth. Catal.* 348: 2148–2154.
- 23 Osborn, J.A. and Wilkinson, G. (1967). *Inorg. Synth. Inorg. Synth.* 10: 67.
- 24 Wilkins, R.G. (1991). *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, 2e. Weinheim: VCH.
- 25 Ramkumar, N. and Nagarajan, R. (2013). *J. Org. Chem.* 78: 2802–2807.
- 26 Sinn, H. and Kaminsky, W. (1980). *Adv. Organomet. Chem.* 18: 99–149.
- 27 Spessard, G. and Miessler, G. (2010). *Organometallic Chemistry*, 2e, 285–289. Oxford University Press.
- 28 Cano-Yelo, H. and Deronzier, A. (1984). *J. Chem. Soc., Perkin Trans. 2*: 1093–1098.
- 29 Cano-Yelo, H. and Deronzier, A. (1987). *J. Photochem.* 37: 315–321.
- 30 Francisco de Azeredo, S.O. and Figueroa-Villar, J.D. (2014). *World J. Pharm. Pharm. Sci.* 3: 1362–1379.
- 31 Narayanan, J.M.R. and Stephenson, C.R.J. (2011). *Chem. Soc. Rev.* 40: 102–113.
- 32 Sabatier, P. and Senderens, J.B. (1902). *Compt. Rend.* 134: 514–516.
- 33 Johansson Seechurn, C.C.C., Kitching, M.O., Colacot, T.J., and Snieckus, V. (2012). *Angew. Chem. Int. Ed.* 51: 5062–5085.
- 34 Li, H., Johansson Seechurn, C.C.C., and Colacot, T.J. (2012). *ACS Catal.* 2: 1147–1164.
- 35 Eisch, J.J. (2002). *Organometallics* 21: 5439–5463.
- 36 G. S. Silverman, P. E. Rakita, *Kirk-Othmer Encyclopedia of Chemical Technology*, doi:<https://doi.org/10.1002/0471238961.0718090719091222.a01>, 2000.
- 37 Kharasch, M.S. and Fields, E.K. (1941). *J. Am. Chem. Soc.* 63: 2316–2320.
- 38 Kharasch, M.S. and Reinmuth, O. (1954). *Grignard Reactions of Nonmetallic Substances*, 1146–1132. New York: Prentice-Hall.
- 39 Kharasch, M.S. and Fuchs, C.F. (1943). *J. Am. Chem. Soc.* 65: 504–507.
- 40 Thomas, A.A., Wang, H., Zahrt, A.F., and Denmark, S.E. (2017). *J. Am. Chem. Soc.* 139: 3805–3821.

- 41 Lennox, A.J.J. and Lloyd-Jones, G.C. (2013). *Angew. Chem. Int. Ed.* 52: 7362–7370.
- 42 Carrow, B.P. and Hartwig, J.F. (2011). *J. Am. Chem. Soc.* 133: 2116–2119.
- 43 Chinchilla, R. and Nájera, C. (2011). *Chem. Soc. Rev.* 40: 5084–5121.
- 44 Selected example of Cu-free Sonogashira reaction:Pu, X., Li, H., and Colacot, T.J. (2013). *J. Org. Chem.* 78: 568–581.
- 45 Selected example of Cu-free Sonogashira reaction:Handa, S., Smith, J.D., Zhang, Y. et al. (2018). *Org. Lett.* 20: 542–545.
- 46 For proposed mechanism of Cu-free Sonogashira:Gazvoda, M., Varant, M., Pinter, B., and Košmrlj, J. (2018). *Nat. Commun.* 9: 4814–4823.
- 47 ICH guideline Q3D on elemental impurities, EMA/CHMP/ICH/353369/2013, <https://www.ema.europa.eu> (accessed 4 March 2019).
- 48 Janowicz, A.H. and Bergman, R.G. (1982). *J. Am. Chem. Soc.* 104: 352–354.
- 49 Hoyano, J.K. and Graham, W.A.G. (1982). *J. Am. Chem. Soc.* 104: 3723–3725.
- 50 For selected publication, see: Caron, L., Campeau, L.-C., and Fagnou, K. (2008). *Org. Lett.* 10: 4533–4536.
- 51 Neufeldt, S.R. and Sanford, M.S. (2012). *Acc. Chem. Res.* 45: 936–946.
- 52 For selected publication, see: Chen, M.S., Prabagaran, N., Labenz, N.A., and White, M.C. (2005). *J. Am. Chem. Soc.* 127: 6970–6971.
- 53 For selected publication, see: Xia, G., Weng, J., Liu, L. et al. (2019). *Nat. Chem.* 11: 571–577.
- 54 Ishiyama, T., Takagi, J., Ishida, K. et al. (2002). *J. Am. Chem. Soc.* 124: 390.
- 55 Sieser, J.E., Maloney, M.T., Chisowa, E. et al. (2018). *Org. Process. Res. Dev.* 22: 527–534.
- 56 Cheung, H., Tanke, R.S., and Torrence, G.P. (2002). Acetic acid. In: *Ullmann's Encyclopedia of Industrial Chemistry*. Weinheim: Wiley-VCH.
- 57 Jones, J.H. (2000). *Platinum Met. Rev.* 44: 94–105.
- 58 Barnard, C.F.J. (2008). *Organometallics* 27: 5402–5422.
- 59 E. K. Rideal (2019), Paul Sabatier – Obituary notices. <https://royalsocietypublishing.org/doi/pdf/10.1098/rsbm.1942.0006> (accessed 12 February 2019).
- 60 Normann, W. (1903). Process for converting unsaturated fatty acids or their glycerides into saturated compounds, DE141029.
- 61 Ojima, I., Tsai, C., Tzamarioudaki, M., and Bonafoix, D. (2004). *Org. React.* <https://doi.org/10.1002/0471264180.or056.01>.
- 62 Whiteker, G.T. and Cobley, C.J. (2012). *Top Organomet. Chem.* 42: 35–46.
- 63 Jira, R. (2009). *Angew. Chem. Int. Ed.* 48: 9034–9037.
- 64 Elschenbroich, C. (2006). *Organometallics*. Weinheim: Wiley-VCH.
- 65 Osborn, J.A., Wilkinson, G., and Young, J.F. (1965). *Chem. Commun.*
- 66 Coffey, R.S. (1968). Hydrogenation process, GB1121643.
- 67 Noyori, R., Ohkuma, T., Kitamura, M. et al. (1987). *J. Am. Chem. Soc.* 109: 5856.
- 68 Ault, A. (2002). *J. Chem. Educ.* 79: 572.
- 69 Knowles, W.S. (2002). *Angew. Chem. Int. Ed.* 41: 1998–2007.
- 70 Jacobsen, E.N., Pfaltz, A., and Yamamoto, H. (eds.) (1999). *Comprehensive Asymmetric Catalysis*, 1443–1445. Berlin; New York: Springer.
- 71 Wittig, G. and Schöllkopf, U. (1954). *Chemische Berichte* 87: 1318.
- 72 N. Yee, X. Wei, C. Senanayake Challenge and opportunity in scaling-up metathesis reaction: synthesis of Ciluprevir (BILN 2061), In *Sustainable*

- Catalysis*, Eds. P. J. Dunn, K. K. (Mimi) Hii, M. J. Krische, M. T. Williams, pp 215-232, 2013, Wiley
- 73 Burns, A.R., Lam, H.W., and Roy, I.D. (2017). *Org. React.* 93: 1.
- 74 Cecchin, G., Morini, G., and Piemontesi, F. (2003). Ziegler–Natta catalysts. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. Wiley-VCH.
- 75 Stephenson, C. and Yoon, T. (2016). *Acc. Chem. Res.* 49: 2059–2060, special edition “Photoredox Catalysis in Organic Chemistry”.
- 76 Shaw, M.H., Twilton, J., and MacMillan, D.W.C. (2016). *J. Org. Chem.* 81: 6898–6926.
- 77 For selected example, see: Huff, C.A., Cohen, R.D., Dykstra, K.D. et al. (2016). *J. Org. Chem.* 81: 6980–6987.
- 78 For selected example, see: Hsieh, H.-W., Coley, C.W., Baumgartner, L.M. et al. (2018). *Org. Process Res. Dev.* 22: 542–550.